

Associations of antidepressant drug pathway proteins between drug efficacy and acceptability outcomes

Emily Liu^{1,2}, Jennifer L. Wilson²

1 Department of Statistics, Brigham Young University

2 Department of Bioengineering, University of California Los Angeles



Abstract

Antidepressant drug therapies provide positive therapeutic outcomes but are also not without unexpected and sometimes negative drug outcomes. Studies have shown that by understanding drug target protein-protein interactions (PPI) and associated phenotypes, scientists can better predict these unexpected drug outcomes. In this project, we use PathFX, a network algorithm that analyzes PPI downstream of drug targets, to investigate the association between network proteins and clinical assessment of antidepressant effects. We applied a linear regression and a regularized linear regression (RLR) model to identify relationships between PathFX-identified drug network genes and clinical outcomes such as efficacy and acceptability. We found that the genes with the highest and lowest coefficients were different between efficacy and acceptability outcomes. Therefore, our results suggest that antidepressant drug network genes associated with high clinical efficacy or acceptability are related but contain distinct network proteins.

PathFX algorithm

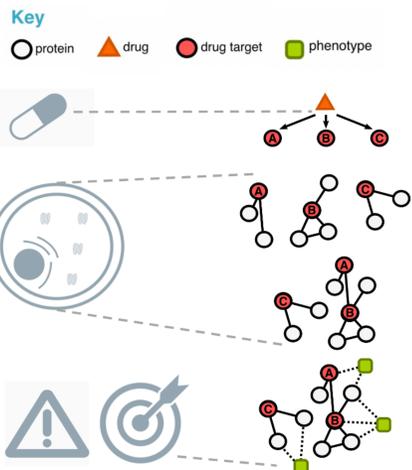


Figure 1: PathFX function

PathFX is an algorithm created to better understand relationships between drug targets and disease phenotypes using local protein-protein interactions (Wilson et al, 2018). PathFX first creates drug networks containing downstream proteins and then identifies associated phenotypes using statistical enrichment. PathFX integrates data drug-to-protein binding information from DrugBank and gene/protein-to-phenotype information from DisGeNet, Phenotype Genotype Integrator (PheGenI), ClinVar, OMIM, and PheWas (Wilson et al., 2018).

Clinical trial data: antidepressants

We used clinical data from a systematic review and network meta-analysis (Cipriani et al., 2018) of 21 antidepressants for the acute treatment of adults with unipolar major depressive disorder. Primary outcomes of the study included efficacy and acceptability, and these were quantified as odds ratios (Table 1).

Using PathFX, we created drug pathway networks to identify drug proteins and associated phenotypes. We see examples of two medications used in the study (Figure 3, Figure 4).

Table 1: Antidepressants and associated efficacy and acceptability outcomes. Table with columns: Drug, Drug Bank ID, Efficacy (OR), Efficacy C.I., Acceptability (OR), Acceptability C.I.

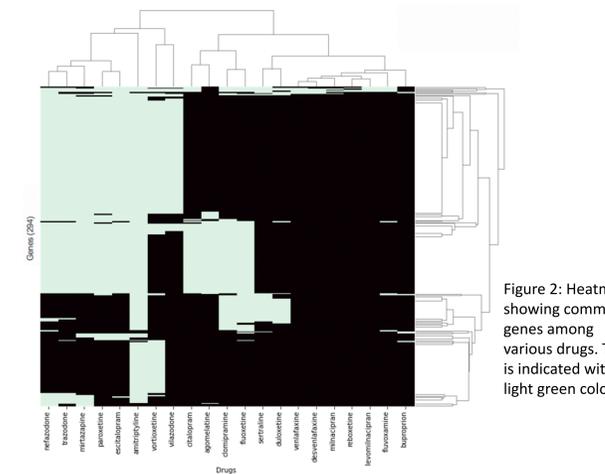


Figure 2: Heatmap showing common genes among various drugs. This is indicated with a light green color.

SNRIs

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are a drug class of antidepressants. These drugs increase the activity of serotonin and norepinephrine in the brain. They also block the reabsorption of these chemicals which helps relieve depression. Milnacipran and desvenlafaxine are two of many SNRIs that are available for approved use today.

Although both milnacipran and desvenlafaxine are SNRIs, their drug-protein pathways look quite different. Through these networks, we can also see that different protein-associated phenotypes exist between these drugs. This illustrates the unique drug-protein pathway networks that exist between antidepressants, even those of the same drug class.

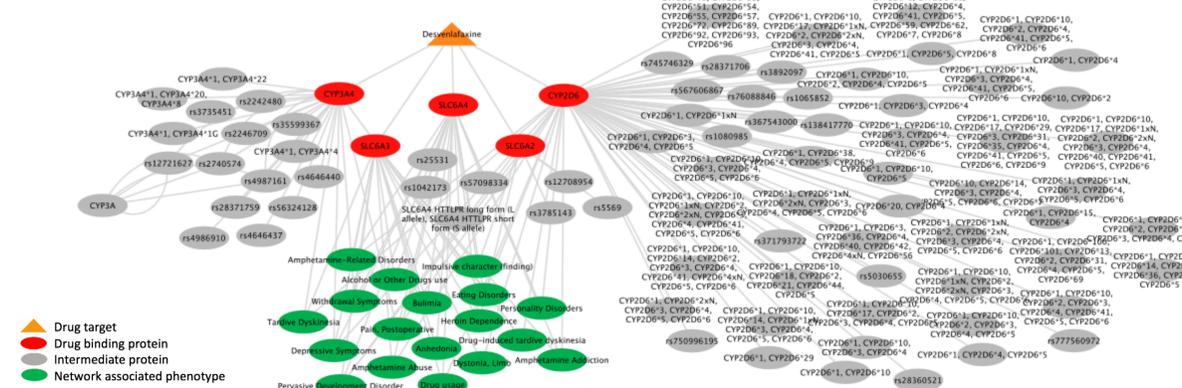


Figure 4: PathFX network of desvenlafaxine

Results

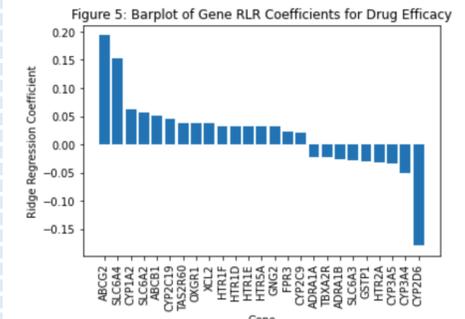


Table 2: Extreme efficacy RLR coefficients. Table with columns: Gene, RLR coefficient. Top: ABCG2, SLC6A4, CYP1A2. Bottom: CYP2D6, CYP3A4, CYP3A5.

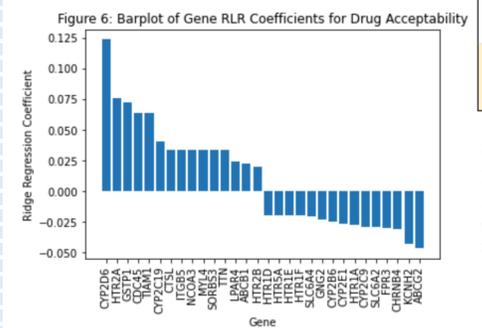


Table 3: Extreme acceptability RLR coefficients. Table with columns: Gene, RLR coefficient. Top: CYP2D6, HTR2A, GSTP1. Bottom: ABCG2, KCNH2, CHRN4.

- 1 ATP-binding cassette family
2 Serotonin-binding genes
3 Cytochrome P450 enzyme family
4 Isozyme genes
5 Potassium channel genes
6 Ligand-gated ion channel genes

In applying RLR to clinical efficacy data, ATP-binding cassette family genes, serotonin-binding genes, and cytochrome enzyme genes (e.g., ABCG2, SLC6A4, and CYP1A2) had the highest, and cytochrome P450 family member genes (e.g., CYP2D6, CYP3A4, and CYP3A5) had the lowest coefficients in the model.

In applying RLR to clinical acceptability data, cytochrome P450 family enzyme genes, serotonin-binding genes, and isozyme genes (e.g., CYP2D6, HTR2A, and GSTP1) had the highest, and forming ligand-gated ion channel genes (e.g., ABCG2, KCNH2, and CHRN4) had the lowest model coefficients.

Discussion

Our results suggest that antidepressant drug network genes associated with high clinical efficacy or acceptability are related but contain distinct network proteins. We learn from previous research that network proteins may have their own associated phenotypes. Therefore, further steps of research may include identifying the shared and unique phenotypes among the genes in this study that most affect antidepressant efficacy and acceptability. This may help scientists better predict which phenotypes may arise when studying the effects of antidepressants.

Special thanks to Dr. Jennifer Wilson and her mentorship on this project.

1. Cipriani, A., (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis, The Lancet, 391(10128):1357-1366
2. Wilson, J., (2018). PathFX provides mechanistic insights into drug efficacy and safety for regulatory review and therapeutic development, PLOS Computational Biology, 14(12):1-27